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(54) Title: USE OF CHOLINESTERASE INHIBITORS FOR TREATING ATTENTION DEFICIT DISORDERS

(57) Abstract

The invention provides the use of cholinesterase inhibitors, particularly acetylcholinesterase inhibitors such as galantamine, in the manufacture of a medicament for combatting attention deficit disorders.

USE OF CHOLINESTERASE INHIBITORS FOR TREATING ATTENTION DEFICIT DISORDERS

The present invention relates to a method of combatting attention deficit disorders (hereinafter referred to as ADD). In particular, the invention relates to the use of a pharmaceutically acceptable cholinesterase inhibitor in the manufacture of a medicament for use in combatting ADD.

Attention deficit disorders affect children, adolescents and adults affecting up to 10% of children and at least 2% of adults. The childhood condition is often known as attention-deficit hyperactivity disorder (ADHD). Symptoms usually first manifest between the ages of 2 - 5. These children have a short attention span, motor hyperactivity, and are disorganised, forgetful and impulsive. ADHD can have a serious effect on the child's academic progress and performance and causes stress to family and teachers and difficulties in interacting with the child's peer group. The condition can persist into adult life. In adults, the major symptoms include distractibility, disorganisation and accident proneness. The condition in adults and children causes serious disruption to normal lifestyle patterns, and creates great stresses to all aspects of daily life, in the home, the workplace and in social situations. ADD as used herein covers both the adult and child forms of the condition, as well as hyperkinetic disorders and disorders which include any of the characterising criteria of the American Psychiatric Association's DSM-IV Classification of the disorders.

Various therapies have been proposed but have not proved satisfactory, due *inter alia* to lack of efficacy and/or undesirable side effects. Stimulants such as dexamphetamine, methylphenidate and pemoline have been

used clinically in the management of ADD. Whilst they have been found to improve the primary manifestations such as motor activity, distractability and impulsivity in some sufferers, their side effects including anorexia, delayed onset of sleep, mood changes and exacerbation of pre-existing psychotic symptoms together with the possible potential for abuse, limits their utility. Other classes of drug such as tricyclic antidepressants have been suggested in the literature but are not generally regarded as being effective agents for the management of ADD. There is accordingly a need for a new therapeutic method for the management of ADD. The present invention provides such a method.

Thus we have surprisingly found that cholinesterase inhibitors such as galantamine can effectively combat ADD.

According to one aspect, the present invention provides a method of combatting ADD comprising administering to a subject a pharmaceutically acceptable cholinesterase inhibitor.

According to a related aspect, the invention provides the use of a pharmaceutically acceptable cholinesterase inhibitor in the manufacture of a medicament for combatting ADD.

As used herein the term 'combatting' includes both therapy and prophylaxis.

The invention encompasses the use of any cholinesterase inhibitor, provided of course that it is pharmaceutically acceptable.

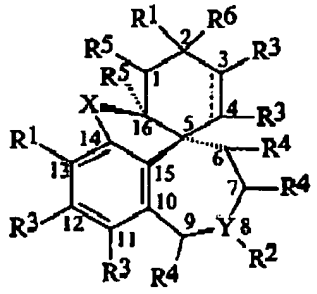
Examples of cholinesterase inhibitors which may be used according to the invention include, but are not limited to, physostigmine, tacrine and tacrine analogues, fasiculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, huperazine, donepezil and pro-drugs of any of these in which the inhibitor is modified in accordance with principles of pro-drug construction known in the art. Examples of such

modifications include the introduction of hydrophilic or lipophilic groups to enhance solubility, or penetration through cell membranes, respectively.

Preferred cholinesterase inhibitors for use according to the invention are acetylcholinesterase inhibitors, particularly those which are capable of crossing the blood brain barrier.

Particularly preferred cholinesterase inhibitors for use according to the invention include galantamine, epigalantamine and norgalantamine, and analogues, salts and derivatives of any of these. Galantamine was previously known as galanthamine. It is a tertiary alkaloid which can be extracted from various snowdrop bulbs e.g. the Caucasian snowdrop galanthus woronowii (Amaryllidaceae) and related species and daffodil bulbs or made by chemical synthesis. It has a high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. It is active substantially selectively at nicotinic receptor sites with substantially little effect on muscarinic receptor sites.

Particularly preferred cholinesterase inhibitors for use in the invention are galantamine and its derivatives of formula (I):



wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R_1 is

independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, C_{1-6}alkoxy, alkylthio, aryloxy, arylthio, R_3-substituted aryloxy, R_3-substituted arylthio, aralkoxy, an optionally R_3-substituted aliphatic or aryl carbamyl group, aralkylthio, R_3-substituted aralkoxy, R_3-substituted aralkylthio, aryloxymethyl, R_3-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_3-substituted benzoyloxy, aryloxycarbonyl and R_3-substituted aryloxycarbonyl,

R_2 is selected from hydrogen, straight or branched chain C_{1-6}alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R_3-substituted phenyl, alkylphenyl, R_3-substituted alkylphenyl, heterocyclyl selected from α- or β-furyl, α- or β-thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy,

each R_3 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R_4 is independently selected from hydrogen, halo, trifluoromethyl or C_{1-4}-alkyl,

each R_5 is independently selected from hydrogen or hydroxymethyl,

R_6 is hydrogen or C_{1-6}alkyl, or when R_1 at carbon atom 2 is hydroxyl, R_6 may be a moiety of formula I wherein R_6 is hydrogen and R_1 is a linking bond; or

R_1 at carbon atom 2 and R_6 may jointly form semicarbazone,

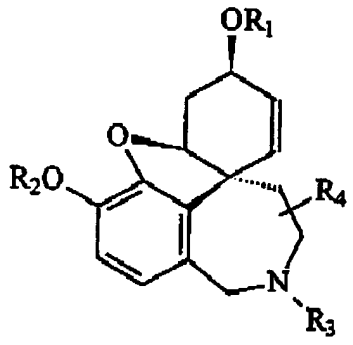
X is oxygen or NR_3,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and pharmaceutically acceptable acid addition salts thereof.

Of the compounds of formula I which may be used in the method of the invention, preferred compounds are those in which the alkyl moieties contain 1 to 8 carbon atoms, halogen atoms are preferably fluorine, bromine, chlorine, aryl moieties are preferably phenyl, cycloalkyl groups are preferably 3- to 7-membered rings, especially cyclopropyl or cyclobutyl, acyl groups are preferably lower alkanoyl groups and heteroaryl moieties are preferably 5- to 8-membered rings, e.g., thienyl, furyl, pyridyl, pyrrolyl, or pyrizanyl.

Preferred compounds of formula I are the compounds of formula II



II

wherein R^1 and R^2 which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

R^4 represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton,

and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

Formula II includes galantamine itself.

Particularly preferred is galantamine itself, and salts thereof such as halides for example galantamine hydrobromide and the use of these compounds in the manufacture of a medicament for combatting ADD provides a further aspect of the invention.

Among these compounds are those described in EP-A-236684 and WO88/08709, the disclosures of which are incorporated herein by reference. Galantamine and its derivatives of formula I and II may be prepared by the methods described in these publications.

The cholinesterase inhibitors for use in the invention include compounds which are functionally similar to galantamine. These are defined herein as compounds which possess an at least 10-fold selectivity, preferably an at least 20-fold selectivity, more preferably an at least 40-fold selectivity, and most preferably an at least 50 fold selectivity, for acetylcholinesterase as opposed to butyryl-cholinesterase, when measured by the in vitro method of Thomsen and Kewitz: Selective Inhibition of Human Acetylcholinesterase by Galantamine in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990), and T. Thomsen, H. Kewitz and O. Pleul, J. Clin. Chem. Clin. Biochem. 26 469-475 (1988). The in vitro test described by Thomsen and Kewitz in Life Sciences, Vol 46, pp 1553-1558 (1990) is the one referred to herein whenever numeric (10-fold, 20-fold, 40-fold) reference to selectivity for acetylcholinesterase as opposed to butyrylcholinesterase is made. According to Thomsen and Kewitz, galantamine hydrobromide, when tested under the

conditions described, shows a 50-fold selectivity; this selectivity value is taken as the "fix-point" whenever in vitro selectivities are discussed herein and could be used, for the purpose of determining the selectivities for other cholinesterase inhibitors, as a calibration value which is the one to establish with galantamine hydrobromide in any repetition of the experiment described by Thomsen and Kewitz. Thus, with reference to this determination method, a preferred acetylcholinesterase inhibitor is one which in the in vitro method described has an at least 10-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, such as an at least 20-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, e.g. an at least 40-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. A selectivity test is commercially available (from Sigma Diagnostics).

For use in the method of the invention the cholinesterase inhibitor such as galantamine and derivatives and salts thereof may be formulated according to conventional methods of pharmacy, together where appropriate with one or more pharmaceutically acceptable carriers, excipients or diluents such as, for example, are described in Remingtons Pharmaceutical Sciences. Such formulations may for example take the form of tablets, capsules, solutions, or lozenges, pessaries, creams, suppositories or transdermal formulations such as patches, creams, ointments or lotions, depending upon the administration route to be used, which may include enterally or parenterally, including orally or injection via the intravenous, intramuscular or subcutaneous routes, or intrathecally by means of an implanted device.

Oral and transdermal administration routes are preferred.

Precise dosage rates and regimes will depend upon

the individual patient and may be determined by the medical practitioner based on individual circumstances. For oral administration doses may be within the range of 5-100 mg per day, such as 2 to 70 mg per day eg. 10 to 30 mg. For transdermal administration galanthamine may be delivered in equivalent daily doses. For parenteral administration, dosages may be in the range of 0.1 to 100 mg per day, such as 5 to 100 mg per day, e.g. 10 to 50 mg per day, including 5 to 30 mg per day; lower dosages are often preferred.

Galantamine and its acid addition salts form crystals. They are generally only sparingly soluble in water at room temperature; therefore, injectable compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 0.1-50 mg/ml, such as 1-50 mg/ml, more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, such as 10-30 mg/ml, especially 20-30 mg/ml of galantamine.

Cholinesterase inhibitors such as galantamine and salts thereof may be used as the sole drug in the management of ADD, or may be used together with other agents useful in managing ADD.

The invention will now be described with reference to the following non-limiting examples.

Example 1

Formulation of tablets containing galantamine

Composition of 1 tablet containing 1 mg galantamine

Galantamine hydrobromide	0.001 g
Calcium phosphate	0.032 g
Lactose	0.005 g
Wheat Starch	0.0056 g
Microcrystalline Cellulose	0.015 g
Talc	0.0007 g
Magnesium Stearate	0.0007 g

Composition of 1 tablet containing 5 mg galantamine

Galantamine hydrobromide	0.005 g
Calcium phosphate	0.024 g
Lactose	0.004 g
Wheat Starch	0.004 g
Microcrystalline Cellulose	0.04 g
Talc	0.002 g
Magnesium Stearate	0.001 g

Composition of 1 tablet containing 10 mg galantamine

Galantamine hydrobromide	0.010 g
Lactose	0.040 g
Wheat Starch	0.0234 g
Microcrystalline Cellulose	0.0374 g
Talc	0.0036 g
Magnesium Stearate	0.0012 g
Gelatin	0.0044 g

Preparation

All the tablets are prepared according to routine tabletting procedures.

Example 2

Treatment of patients suffering from ADD

Three patients aged 9 to 11 years diagnosed as having ADD were treated with 5 mg of galantamine given 3 times per day for a total of 14 days. After this period of time, the patients showed marked improvement of symptoms, particularly as regards attention and restlessness, as judged on an ecological behavioural scale (translated: Barkley, RA et al, Assessing situational variation in children's problem behaviours: The Home and School Situations Questionnaires, in RJ Prinz (Ed), Advances in Behavioural Assessment of Children and Families, vol 3, pp 157-176, Greenwich, CT, JAI Press, Inc).

A further cohort of two 5 year old patients with ADD have been treated and again symptoms have generally improved, especially attention, as measured by ANT (Amsterdam Neuropsychological Tests), which are standard tests that measure reaction times for different tasks.

The protocol in this case is first a baseline testing before medication and retesting after 2 days on medication and then after a week repeated testing. Ecological scales were also used before and are now being evaluated after one week after two weeks etc. for a treatment of one month duration. The following table shows a selection of results obtained for these two children before and after treatment with galantamine.

	Before:				After:			
	mean	Sd	miss[1]	Fa[2]	mean	Sd	miss	Fa
Patient A								
Baseline:	685	766			727	470		
GoNoGo	705	158	1	1	655	173	1	2
Sustained Att.	1302	565	14	13	1222	472	4	6
Focused Att.	1214	404			1352	434	0	
Patient B								
Baseline:	1051	899			780	418		
GoNoGo	804	162	2	9	766	172	3	3
Sustained Att.	1444	721	31	29	1152	600	20	50
Focused Att.	2444	1367	1		1166	270	3	

[1] Missed task

[2] Failed attempt

This data was normalized and submitted to error analysis that showed an improvement in attention (reduction in time (msec) to complete certain tasks and with fewer errors) over 2.5 standard deviations after medication with galantamine hydrobromide 2.5 mg 3 times a day.

CLAIMS

1. The use of a pharmaceutically acceptable cholinesterase inhibitor or a pro-drug therefor in the manufacture of a medicament for combatting attention deficit disorders.

2. The use is claimed in claim 1 wherein the disorder is attention deficit hyperactivity disorder.

3. The use as claimed in claim 1 wherein the disorder is a hyperkinetic disorder.

4. The use as claimed in any one of the preceding claims wherein the cholinesterase inhibitor is an acetyl cholinesterase inhibitor.

5. The use as claimed in any one of the preceding claims wherein the cholinesterase inhibitor is active substantially selectively at nicotinic receptor sites.

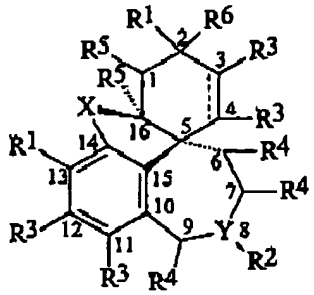
6. The use as claimed in any one of the preceding claims wherein the cholinesterase inhibitor is capable of crossing the blood brain barrier.

7. The use as claimed in any one of claims 1 to 4 wherein the cholinesterase inhibitor is slected from physostigmine, tacrine and tacrine analogues, fasiculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, huperazine, donepezil and pro-drugs of any of these.

8. The use is claimed in any one of claims 1 to 6 wherein the cholinesterase inhibitor is selected from glantamine, epigalantamine and norgalantamine, and

analogues, salts and derivatives of any of these.

9. The use as claimed in any of the preceding claims wherein the cholinesterase inhibitor is selected from galantamine and its derivatives of formula (I):



wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R_1 is independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, C_{1-6}alkoxy, alkylthio, aryloxy, arylthio, R_3-substituted aryloxy, R_3-substituted arylthio, aralkoxy, an optionally R_3-substituted aliphatic or aryl carbamyl group, aralkylthio, R_3-substituted aralkoxy, R_3-substituted aralkylthio, aryloxymethyl, R_3-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_3-substituted benzoyloxy, aryloxycarbonyl and R_3-substituted aryloxycarbonyl,

R_2 is selected from hydrogen, straight or branched chain C_{1-6}alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R_3-substituted phenyl, alkylphenyl, R_3-substituted alkylphenyl, heterocyclyl selected from α- or β-furyl, α- or β-thienyl, thenyl,

pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy,

each R_3 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R_4 is independently selected from hydrogen, halo, trifluoromethyl or C_{1-4}-alkyl,

each R_5 is independently selected from hydrogen or hydroxymethyl,

R_6 is hydrogen or C_{1-6}alkyl, or when R_1 at carbon atom 2 is hydroxyl, R_6 may be a moiety of formula I wherein R_6 is hydrogen and R_1 is a linking bond; or

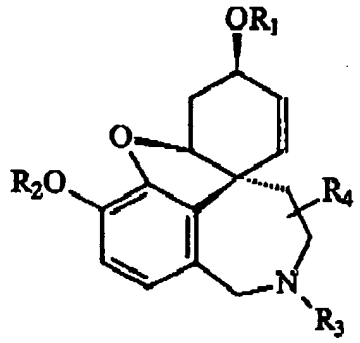
R_1 at carbon atom 2 and R_6 may jointly form semicarbazone,

X is oxygen or NR_3,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and pharmaceutically acceptable acid addition salts thereof.

10. The use as claimed in any one of the preceding claims wherein the cholinesterase inhibitor is selected from compounds of formula II



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wherein R^1 and R^2 which may be the same or different

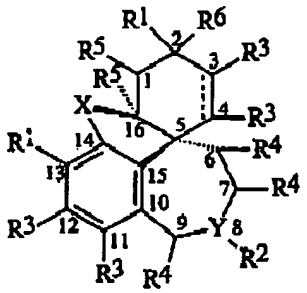
each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

R^4 represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton, and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

11. The use according to any one of the preceding claims where the cholinesterase inhibitor is galantamine or a salt thereof.

12. The use of galantamine or a derivative thereof of formula I:



wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R_1 is independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano,

sulfhydryl, C_{1-6}alkoxy, alkylthio, aryloxy, arylthio, R_3-substituted aryloxy, R_3-substituted arylthio, aralkoxy, an optionally R_3-substituted aliphatic or aryl carbamyl group, aralkylthio, R_3-substituted aralkoxy, R_3-substituted aralkylthio, aryloxymethyl, R_3-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_3-substituted benzoyloxy, aryloxycarbonyl and R_3-substituted aryloxycarbonyl,

R_2 is selected from hydrogen, straight or branched chain C_{1-6}alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R_3-substituted phenyl, alkylphenyl, R_3-substituted alkylphenyl, heterocyclyl selected from α- or β-furyl, α- or β-thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy,

each R_3 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

each R_4 is independently selected from hydrogen, halo, trifluoromethyl or C_{1-4}-alkyl,

each R_5 is independently selected from hydrogen or hydroxymethyl,

R_6 is hydrogen or C_{1-6}alkyl, or when R_1 at carbon atom 2 is hydroxyl, R_6 may be a moiety of formula I wherein R_6 is hydrogen and R_1 is a linking bond; or

R_1 at carbon atom 2 and R_6 may jointly form semicarbazone,

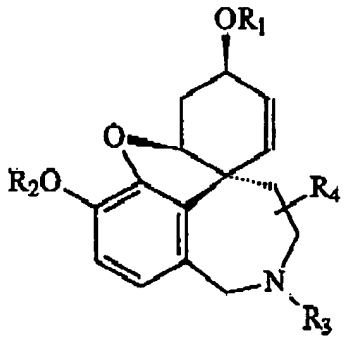
X is oxygen or NR_3,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof and

pharmaceutically acceptable acid addition salts thereof in the manufacture of a medicament for combatting attention deficit disorders.

13. The use of galantamine or a derivative thereof of formula II



II

wherein R^1 and R^2 which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

R^4 represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton,

and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide in the manufacture of a medicament for combatting attention deficit disorders.

14. The use of galantamine or a salt thereof in the

manufacture of a medicament for combatting attention deficit disorders.

15. A method of combatting attention deficit disorders comprising adinistering a pharmaceutically acceptable cholinesterase inhibitor or a pro-drug therefor.

16. A method as claimed in claim 15 wherein the disorder is as defined in claim 2 or claim 3.

17. A method as claimed in claim 15 or claim 16 wherein the cholinesterase inhibitor is as defined in any one of claims 4 to 14.

INTERNATIONAL SEARCH REPORT

Inter[redacted] Application No
PCT/[redacted] 98/02378

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/27 A61K31/66 A61K31/44 A61K31/445 A61K31/40
A61K31/645 A61K31/435 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 39000 A (EISAI CO LTD ;ROGERS SHARON L (US)) 11 September 1998 see the whole document ---	1-7, 15-17
P,X	WO 97 46527 A (EISAI CO LTD) 11 December 1997 see abstract see page 27, last paragraph - page 28, last paragraph; claims 1,79-87 ---	1-7, 15-17
X	EP 0 515 302 A (SNORRASON ERNIR) 25 November 1992 see abstract	1,4-6, 8-15,17
Y	see page 15, line 22 - line 55; claims 1,4,8-21,24 ---	2,3
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
8 December 1998	22/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

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INTERNATIONAL SEARCH REPORT

Inter[illegible]plication No
PCT/G[illegible]8/02378

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 92 20328 A (SNORRASON ERNIR) 26 November 1992 see abstract see claims 1,5,8-18,21-27	1-6,8-17
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X	EP 0 229 391 A (EISAI CO LTD) 22 July 1987 see abstract see page 12, line 18 - page 13, line 1 see page 15, line 7 - line 11 see page 49, line 10 - line 27; table 3	1,2,4-6, 15-17

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Inter[illegible]plication No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 0 411 534 A (WARNER LAMBERT CO) 6 February 1991 see abstract see page 2, line 1 - line 12 see page 3, line 1 - line 43; claims 1,5	1,3-7, 15-17
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INTERNATIONAL SEARCH REPORT

I. [redacted]nal application No.
PCT/GB 98/02378

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15-17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 15-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ GB 98/02378

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are theoretically contained within the definition "cholinesterase inhibitor" of claims 1 and 15, the search had to be restricted on economic grounds to the general idea of the invention and to the compounds mentioned in claims 7-14 (Art. 6 PCT; Guidelines Part B, Chapt. II.7 last sentence and Chapter III, 3.7).

Claims searched completely: 7-14
Claims searched incompletely: 1-6, 15-17

INTERNATIONAL SEARCH REPORT

Inter[illegible]pplication No
PCT/GB 98/02378

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